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stimulate or enhance antibody production in a subject, and a pharmaceutically acceptable carrier, wherein the conjugation of the ganglioside involves a ceramide double bond of the ganglioside and an aminolysl group of Keyhole Limpet Hemocyanin or a derivative thereof.-

REMARKS

Claims 69-86 were pending in the subject application. Applicants have hereinabove amended claim 69 and added new claims 87-96. Applicants contend that these claims do not involve any issue of new matter. Support for this amendment may be found inter alia in the specification on page 32, line 1 to page 33, line 10. Accordingly, claims 69-96 will be pending upon the entry of this amendment.

Double Patenting

The Examiner provisionally rejected claims 69-86 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims 53-71 of copending Application No. 08/477,097.

The Examiner stated that applicants assert that the added new claims in the copending application obviate the obvious type double patenting. The Examiner stated that applicants arguments are not persuasive since the claims of the copending application encompass conjugating the ceramide portion of GM2 and GD2 to a KLH and a carbohydrate derivable from the bark of a saponaria Molina tree (i.e. QS-21).

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully point out that the claims in U.S. Serial No. 08/477,097 have been amended. The claims in the subject application are drawn to a composition comprising a GM2 or a GD2 ganglioside conjugated through the ceramide portion of the ganglioside to Keyhole Limpet Hemocyanin

or a derivative thereof and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree, the amounts of such conjugated ganglioside and such carbohydrate being effective to stimulate or enhance antibody production in a subject, and a pharmaceutically acceptable carrier, wherein the conjugation of the ganglioside is through a ceramide-derived carbon. In contrast, the claims in copending application no. 08/477,097 are drawn to a composition comprising a GM2 or GD2 ganglioside conjugated through the ceramide portion of the ganglioside to an immunogenic protein-based carrier and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree, the amounts of such conjugated ganglioside and such carbohydrate being effective to stimulate or enhance antibody production in a subject, and a pharmaceutically acceptable carrier ,wherein the immunogenic protein-based carrier is Keyhole Limpet Hemocyanin or a derivative thereof. Accordingly, applicants contend that the an obviousness-type double patenting rejection is not appropriate since the claims of the subject application involve a conjugation to KLH or a derivative thereof. The claims of copending 08/477,097 involve a conjugation to an immunogenic protein-based carrier. Accordingly, applicants contend that are patentable over the claims of 08/477,097 since an immunogenic-protein based carrier would not render obvious KLH or derivative thereof.

The Examiner provisionally rejected claims 69-86 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 53-72 of copending Application Nos. 08/475,784. The Examiner stated that applicants assert that the added new claims in the copending application obviate the obvious type double patenting. The Examiner stated that applicants arguments are not persuasive since the claims of the copending application encompass conjugating the ceramide portion of GM2 or GD2 to a KLH and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree (i.e. QS-21).

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully point out that the claims in 08/475,784 have been amended. The claims in the subject application are drawn to a composition comprising a GM2 or a GD2 ganglioside conjugated through the ceramide portion of the ganglioside to Keyhole Limpet Hemocyanin or a derivative thereof and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree, the amounts of such conjugated ganglioside and such carbohydrate being effective to stimulate or enhance antibody production in a subject, and a pharmaceutically acceptable carrier, wherein the conjugation of the ganglioside is through a ceramide-derived carbon. In contrast, the claims in copending application no. 08/475,784 are drawn to a composition comprising a ganglioside conjugated through the ceramide portion of the ganglioside to Keyhole Limpet Hemocyanin or a derivative thereof and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree, the amounts of such conjugated ganglioside and such carbohydrate being effective to stimulate or enhance antibody production in a subject, and a pharmaceutically acceptable carrier, wherein the ganglioside is selected from the group consisting of GM2, GM3, GD3, GD3 lactone, O-acetyl GD3 and GT3. Accordingly, applicants contend that an obviousness-type double patenting rejection is not appropriate. Accordingly, applicants contend that the an obviousness-type double patenting rejection is not appropriate since the claims of the subject application involve a GM2 or GD2 ganglioside, while the claims of copending 08/475,784 involve a ganglioside. Accordingly, applicants contend that are patentable over the claims of 08/475,784 since an ganglioside would not render obvious GM2 or GD2.

Nevertheless, without conceding the correctness of the Examiner's position but to expedite the prosecution of the subject application, applicants will consider filing a terminal disclaimer, if it is still deemed necessary in light of the above

amendments and remarks, upon the indication of allowable subject matter. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Claim Rejections - 35 USC § 112

The Examiner rejected claims 69-71, and 73-86 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed 6/10/96.

The Examiner stated that applicants' amendment is sufficient to obviate the objection to the specification for: 1) the use of other gangliosides or chemically modified gangliosides; and 2) use of the claimed product as a vaccine. However, the Examiner stated that the specification provides insufficient guidance of how to use derivatives of KLH as recited. The Examiner stated that applicants assert that by routine experimentation one skilled in the art is enabled to make derivatives of KLH. The Examiner stated that applicants assert that the derivatives of KLH can be tested using the KLH disclosed in the specification. The Examiner stated that applicants arguments are not persuasive.

The Examiner stated that protein chemistry is probably one of the most unpredictable areas of biotechnology. The Examiner stated that for example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). The Examiner stated that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while

replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). The Examiner stated that Rudinger et al. teaches "particular amino acids and sequences for different aspects of biological activity can not be predicted a priori, but must be determined from case to case by painstakingly experimental study." The Examiner stated that Salgaller et al teach modifications (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein. The Examiner stated that Fox et al. teach methods for determining fragments which have antigenic activity is unpredictable. The Examiner stated that these references demonstrate that an even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. The Examiner stated that in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad or derivatives and fragments encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

The Examiner stated that contrary to applicants arguments, it is reasonable to conclude an undue burden is required to screen for positions within the sequence where amino acid modifications (i.e. additions, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility are limited and the result of such modifications is unpredictable as exemplified by the teachings of Lazar et al., Burgess et al., Rudinger et al., and Salgaller et al. The Examiner stated that these references demonstrate that an even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein.

The Examiner stated that the specification does not support the

broad scope of the claims which encompass a multitude of analogs or equivalents because the specification does not disclose the following:

-the general tolerance to modification and extent of such tolerance;

-specific positions which can be predictably modified; and

-the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

The Examiner stated that the applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims broadly including any number of deletions, additions, and/or substitutions of any size. The Examiner stated that the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The Examiner stated that without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The Examiner stated that see Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

The Examiner stated that applicants cite to page 12, lines 4-13 of the specification for support of using derivatives of KLH. The Examiner stated that said disclosure is not commensurate in scope with the claimed invention. The Examiner stated that said cite makes reference only to linking KLH to an "immunological adjuvant" and not amino acid modifications (i.e. deletions, substitutions) of KLH. The Examiner stated that as set forth above the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The Examiner stated that for the reasons set forth above

and in the last Office Action said rejection is maintained.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the claimed invention is enabled. Applicants maintain that the specification provides sufficient teachings which enable one skilled in the art to generate such derivatives. See Specification page 12, lines 4-13. Applicants also described some routine experiments on page 4, second paragraph of the January 6, 1997 Supplemental Communication in Response to June 10, 1996 Office Action to generate said derivatives. Regarding the Examiner's specific comments about the variation of one or a few amino acids which may change the property of a protein, the disclosed specification has provided specific embodiments of Keyhole Limpet Hemocyanin being used as the immunogenic protein. The derivatives generated may easily be tested using the specific Keyhole Limpet Hemocyanin disclosed in the specification for comparison. Accordingly, there is no undue experimentation and applicants maintain that the derivatives of Keyhole Limpet Hemocyanin are fully enabled by the specification as filed. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Claim Rejections - 35 USC § 103

The Examiner rejected claims 69-81, and 83-86 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663) and Ritter et al. (1990) and further in view of Kensil et al and Marciani et al. for the reasons set forth in the Office Action mailed 6/13/96.

The Examiner stated that applicants appear to argue the rejection should be withdrawn since the prior art does not suggest or provide an expectation of conjugating the ganglioside to the KLH through the ceramide portion of the ganglioside. The Examiner

stated that applicants arguments are not persuasive. The Examiner stated that Ritter et al. (1991) teaches conjugating GM2 to KLH gives specific antibodies to GM2. The Examiner stated that additionally Ritter et al. 1991 teaches the gangliosides differ most obviously from each other in their carbohydrate moieties. The Examiner stated that accordingly, it would have been expected the KLH is bound to the ceramide portion, particularly since the antibodies of the ganglioside bind to the hydrophilic portion (i.e. carbogydrate portion) as exemplified by Ritter et al. 1990 who sets forth that alteration of the carbohydrate moiety affects binding of antibody.

The Examiner stated that applicants assert the prior art does not teach of composition comprising a carbohydrate derivable from the bark from the tree as recited. The Examiner stated that applicants arguments are not persuasive in view of the teaches of Kensil et al who sets forth using QS-21 which was purified from Quillaja saponaria Molina. The Examiner stated that applicants assert that the prior art does not teach of the ganglioside conjugate. The Examiner stated that applicants argument is not persuasive for the reasons set forth above.

In response, applicants respectfully traverse the Examiner's above rejections. Applicants contend that the cited references do not teach, suggest or disclose applicants claimed invention. Nevertheless, without conceding the correctness of the Examiner's position but to expedite the prosecution of the subject application, applicants have hereinabove amended and added new claims to further specify the conjugation. Applicants contend that none of the cited references alone or in combination teach the claims that will be pending upon entry of this amendment. Specifically, the amended and new claims now specify that the conjugation of the ganglioside is through: (a) a ceramide-derived carbon, (b) carbon derived from a cleavage of a double bond in the ceramide portion of the ganglioside, (c) carbon derived from

a ceramide double bond to Keyhole Limpet Hemocyanin or a derivative thereof, (d) ceramide double bond of the ganglioside and a reactive amine group of Keyhole Limpet Hemocyanin or a derivative thereof, or (e) ceramide double bond of the ganglioside and an aminolysl group of Keyhole Limpet Hemocyanin or a derivative thereof. Applicants contend that the cited references alone or in combination do not teach, suggest or disclose the subject of these claims. Applicants contend that these remarks and amendments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Rejection Under 35 U.S.C. 103(a)- Claim 82

The Examiner rejected claim 82 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Livingston et al., Kensil et al and Marciani et al. as applied to claims 69-81, and 83-86 above and further in view of Irie et al. The Examiner stated that Livingston et al. (Cancer Research), Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Livingston et al., Kensil et al nor Marciani et al. do not teach of administering the vaccine for treating cancer of epithelial origin. The Examiner stated that Irie et al. teachings are set forth in the Office Action mailed 6/13/96. The Examiner stated that one of ordinary skill in the art to administer the vaccine to patient afflicted with or susceptible to cancer of epithelial origin in view of the reasons set forth in Office Action mailed 6/13/96. The Examiner stated that applicants appear to argue the rejection should be withdrawn since the prior art does not suggest or provide an expectation of making the claimed invention as applied to the claims above. The Examiner stated that for the reasons set forth above applicants arguments are not persuasive.

In response, applicants respectfully traverse the Examiner's

above rejections. Applicants contend that the cited references do not teach, suggest or disclose applicants claimed invention. The Examiner stated the following in reference to the teachings of Kensil, Marciani and Irie in the Office Action dated June 13, 1996 that Kensil teaches that QS21 produced a higher antibody response than aluminum hydroxide and that the immune responses obtained with QS21 reached a plateau at doses between 10 and 80 ug in mice. The Examiner stated that Marciani teaches the use of QS21 as an adjuvant in a vaccine at concentrations of 10 and 20 ug, and that the QS21 adjuvant did not cause a toxic reaction in cats. The Examiner stated that Irie teaches that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas. Applicants contend that none of these references alone or in combination the information missing ib Livingston and Ritter (as stated above) that might render the claimed invention obvious. The new claims further specify conjugation and none of the cited references suggests these conjugations. Nevertheless, without conceding the correctness of the Examiner's position but to expedite the prosecution of the subject application, applicants have hereinabove added new claims to further specify the conjugation. Applicants contend that none of the cited references alone or in combination teach the claim that will be pending upon entry of this amendment. Specifically, the new claims now specify that the conjugation of the ganglioside is through: (a) a ceramide-derived carbon, (b) carbon derived from a cleavage of a double bond in the ceramide portion of the ganglioside, (c) carbon derived from a ceramide double bond to Keyhole Limpet Hemocyanin or a derivative thereof, (d) ceramide double bond of the ganglioside and a reactive amine group of Keyhole Limpet Hemocyanin or a derivative thereof, or (e) ceramide double bond of the ganglioside and an aminolysl group of Keyhole Limpet Hemocyanin or a derivative thereof. Applicants contend that these remarks and amendments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Summary

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection and earnestly solicit allowance of the claims now pending in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any other is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Albert Wai-Kit Chan

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Albert Wai-Kit Chan 7/21/99

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